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2018-10-01

Piitulainen , H , Illman , M , Laaksonen , K , Jousmäki , V & Forss , N 2018 , ' Reproducibility of corticokinematic coherence ' , NeuroImage , vol. 179 , pp. 596-603 . https://doi.org/10.1016/j.neuroimage.2018.06.

http://hdl.handle.net/10138/304111
https://doi.org/10.1016/j.neuroimage.2018.06.078

publishedVersion

NeuroImage 179 (2018) 596–603

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Reproducibility of corticokinematic coherence

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ARTICLE INFO

Keywords:
Proprioception
Movement evoked field
Kinematics
Magnetoencephalography
Somatosensory
Repeatability

ABSTRACT

Corticokinematic coherence (CKC) between limb kinematics and magnetoencephalographic (MEG) signals reflects cortical processing of proprioceptive afference. However, it is unclear whether strength of CKC is reproducible across measurement sessions. We thus examined reproducibility of CKC in a follow-up study.

Thirteen healthy right-handed volunteers (7 females, 21.7 ± 4.3 yrs) were measured using MEG in two separate sessions 12.6 ± 1.3 months apart. The participant was seated and relaxed while his/her dominant or non-dominant index finger was continuously moved at 3 Hz (4 min for each hand) using a pneumatic movement actuator. Finger kinematics were recorded with a 3-axis accelerometer. Coherence was computed between finger acceleration and MEG signals. CKC strength was defined as the peak coherence value at 3 Hz form a single sensor among 40 pre-selected Rolandic gradiometers contralateral to the movement.

Pneumatic movement actuator provided stable proprioceptive stimuli and significant CKC responses peaking at the contralateral Rolandic sensors. In the group level, CKC strength did not differ between the sessions in dominant (Day-1 0.40 ± 0.19 vs. Day-2 0.41 ± 0.17) or non-dominant (0.35 ± 0.16 vs. 0.36 ± 0.17) hand, nor between the hands. Intraclass-correlation coefficient (ICC) values indicated excellent inter-session reproducibility for CKC strength for both dominant (0.86) and non-dominant (0.97) hand. However, some participants showed pronounced inter-session variability in CKC strength, but only for the dominant hand.

CKC is a promising tool to study proprioception in long-term longitudinal studies in the group level to follow, *e.g.*, integrity of cortical proprioceptive processing with motor functions after stroke.

1. Introduction

Corticokinematic coherence (CKC) quantifies the coupling between oscillatory cortical activity, measured with electroencephalography (EEG) or magnetoencephalography (MEG), and limb kinematics (*e.g.* acceleration) during repetitive rhythmic voluntary (Bourguignon et al., 2011; Jerbi et al., 2007) and passive (Piitulainen et al., 2013a, 2015, 2018) movements. CKC peaks at the movement frequency and its harmonics, and it can be measured using various peripheral movement-related signals and motor tasks (Piitulainen et al., 2013b). CKC primarily reflects proprioceptive processing in the primary sensorimotor (SM1) cortex (Bourguignon et al., 2015; Piitulainen et al., 2013a) with an apparent latency of 50–100 m s that corresponds to the timing of the strongest deflection of the cortical movement-evoked field (Piitulainen et al., 2015). In addition to hand, CKC can be measured using passive ankle (Piitulainen et al., 2018) or toe movements (Piitulainen et al., 2015).

Potential clinical use of CKC would be the evaluation of the integrity of cortical proprioceptive processing with motor functions after stroke or other type of lesions, and during the recovery. Strength of CKC could be used to monitor changes in the cortical proprioception providing the clinicians with essential information to better target the rehabilitation to restore upper and lower limb function. Furthermore, CKC could reveal insights of cortical proprioceptive processing in response to development and aging related sensorimotor impairments (cerebral palsy, neuropathy, spinal cord injury, etc.). Another potential clinical use is non-invasive,

Abbreviations: CKC, corticokinematic coherence; ICC, intraclass-correlation coefficient; EEG, electroencephalography; MEG, magnetoencephalography; SM1, primary sensorimotor cortex.

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https://doi.org/10.1016/j.neuroimage.2018.06.078
Received 29 March 2018; Received in revised form 25 June 2018; Accepted 28 June 2018
Available online 30 June 2018

pre-surgical functional mapping of SM1 cortex in MEG (Bourguignon et al., 2013). CKC can be used to identify the SM1 cortex (Bourguignon et al., 2011), even in the presence of strong magnetic artifacts arising, e.g., from cranial clips (Bourguignon et al., 2016).

First CKC studies were conducted by using voluntary or experimenter-evoked-passive movements (Bourguignon et al., 2011; Piitulainen et al., 2013a, 2013b). Kinematics of human-made movements are not stable, but vary between consecutive movements, sessions, days, and experimenter. To overcome this issue, a precise computer-controlled MEG--compatible-movement actuator was developed, to produce consistent kinematics across stimuli and individuals (Piitulainen et al., 2015). However, it remains unclear whether CKC is suitable for longitudinal studies. Stability of CKC across time is a prerequisite to use CKC to unravel and follow-up proprioception-related neuronal mechanisms in, e.g., aging, motor-skill acquisition, rehabilitation, stroke recovery, and motor-disorder etiology.

Our aim was to examine the reproducibility of the CKC strength for passive-index-finger movements evoked by a computer-controlled pneumatic movement actuator in a one-year follow-up study. A long enough follow-up period was chosen, since detectable adaptations of cortical proprioceptive processing are in most cases expected to occur in time-rages of months or years. We also aimed to examine whether the CKC strength or its reproducibility differs between the dominant and non-dominant hand. Finally, we evaluated whether inter-individual variation in CKC strength is related to kinematics of the movement stimuli or amplitude of the respective steady-state field amplitude.

2. Materials and methods

2.1. Participants

We studied 13 healthy right-handed volunteers (mean ± SD, age 21.7 ± 4.3 y, 7 females) who did not report any history of movement disorders or neuropsychiatric disease. Their Edinburgh handedness inventory score (Oldfield, 1971) was 87.2 ± 11.4 on the scale from −100 to 100. The study had prior approval by the ethics committee of Aalto University. The participants gave informed consent before participation.

2.2. Experimental protocol

A custom-made non-magnetic pneumatic movement actuator built at Aalto NeuroImaging was used to generate passive dominant and non-dominant index finger flexion-extension movements of the metacarpophalangeal joint. For detailed description of the movement actuator see (Piitulainen et al., 2015). Index finger was attached to a pneumatic artificial muscle (DMSP-10-100 AM-CM, Festo AG & Co, Esslingen, Germany) that moved downward in vertical direction when its internal air pressure was increased to 4 bar thus flexing the finger, and then extending it back to the initial position when the air pressure was released. In this way, continuous passive flexion–extension movements were generated at 3 Hz for the dominant and non-dominant index finger separately (4 min for each finger in separate sessions). The movement range was ~5 mm. Movement at 3 Hz was selected as it has been found applicable and efficient for robust CKC recordings (Piitulainen et al., 2015) still with distinct range of motion and continuous nature of the movement that resembles voluntary repetitive movements.

During the MEG recordings, the participant was sitting with the stimulated hand on the upper plate of the movement actuator that was placed on the table in front of him/her (Fig. 1). The index finger was taped to the aluminum end of the pneumatic muscle. The other hand was resting on the thigh. Earplugs were used to minimize slight concomitant auditory noise that arose from the airflow within the pneumatic muscle. A white A3-sized cardboard sheet was taped horizontally to the MEG gantry to prevent the participant from seeing the moving finger. Participants were instructed to fixate, through a rectangular hole in the cardboard sheet, on a picture on the wall of the magnetically shielded room

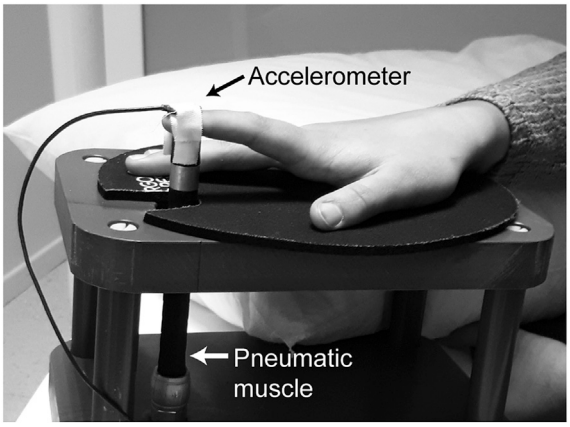

Fig. 1. The experimental setup. The participant's index finger was taped to the vertically moving pneumatic muscle, and an accelerometer was taped on the nail of the finger.

(MSR), 2.2 m in front of the eyes. In order to estimate reproducibility of CKC, the recordings (Day-1) were repeated on average 12.6 ± 1.3 months later (Day-2).

2.3. Measurements

2.3.1. MEG

The measurements were carried out at the MEG Core, Aalto NeuroImaging, Aalto University (Espoo, Finland). MEG signals were recorded in a MSR (Imedco AG, Hägendorf, Switzerland) with a 306-channel whole-scalp neuromagnetometer (Elekta Neuromag™, Elekta Oy, Helsinki, Finland). The recording passband was 0.1–330 Hz and the signals were sampled at 1 kHz. The participant's head position inside the MEG helmet was continuously monitored by feeding currents to five head-tracking coils located on the scalp; the locations of the coils with respect to anatomical fiducials were determined with an electromagnetic tracker (Fastrak, Polhemus, Colchester, VT, USA). EEG was recorded simultaneously with a MEG-compatible EEG cap (ANT Neuro waveguard™ original, Berlin, Germany), containing 60 Ag-AgCl surface electrodes mounted according to the international 10–20 system with modified combinatorial nomenclature (EEG data will be reported elsewhere).

2.3.2. Acceleration

Index finger accelerations were recorded with a 3-axis accelerometer (ADXL335 iMEMS Accelerometer, Analog Devices Inc., Norwood, MA, USA) attached on the nail of the moved finger. Acceleration was low-pass filtered at 330 Hz and sampled at 1 kHz, time-locked to the MEG signals.

2.4. Data processing

2.4.1. Preprocessing

Continuous MEG data were first preprocessed off-line using temporal signal-space-separation with head movement compensation to suppress external interferences, to correct for head movements and to transfer the coordinates to average (the average of the Day-1 and Day-2 coordinates) reference head position (Taulu and Simola, 2006). The MEG and acceleration signals were band-pass filtered offline at 0.5–195 Hz.

2.4.2. Coherence analysis

All analyses were carried out on sensor level. For coherence analyses, the continuous data were split into 2-s epochs with 1.6-s epoch overlap, leading to frequency resolution of 0.5 Hz (Bortel and Sovka, 2007). MEG epochs with magnetometer signals >3 pT or gradiometer signals >0.7 pT/cm were excluded to avoid contamination by eye movements and blinks, muscle activity, or external MEG artifacts. We then performed

coherence analysis (Halliday et al., 1995)—yielding cross-, power- and coherence spectra, as well as cross-correlograms—between MEG signals and the Euclidian norm of the three orthogonal accelerometer signals. Before the coherence analysis, each epoch of acceleration was normalized by its Euclidian norm (Bourguignon et al., 2011).

Peak CKC strength was quantified as the strongest coherence value at 3-Hz among 40 pre-selected Rolandic MEG gradiometers contralateral to the movement. This single sensor was defined independently for Day-1 and Day-2 data. The same approach was used also in the first harmonic of the movement frequency (at 6-Hz). Detailed CKC results here are reported only for the 3 Hz-movement frequency. In addition, we examined whether the channel selection approach affects the reproducibility of CKC. The average CKC value at 3-Hz was computed also for the sensor showing the strongest CKC (mean of a gradiometer pair) and a selection of 30-gradiometers over the contralateral hand area of the SM1 cortex. The topographic distribution of CKC grand average was visualized in the group level for the mean gradiometer pair values using FieldTrip software (Oostenveld et al., 2011).

2.4.3. Steady-state field amplitude and finger kinematics

MEG and acceleration signals, recorded during the passive continuous 3-Hz movements, were averaged with respect to the movement onsets for each individual separately. The resulting steady-state fields were filtered through 1–40 Hz, and acceleration through 1–195 Hz. Then, peak-to-peak amplitude of the steady-state field was computed for dominant and non-dominant hands separately using the same MEG sensor as in the coherence analysis. Similarly, magnitude and regularity of the evoked movements were estimated by computing the mean and coefficient of variation of peak acceleration magnitude (*i.e.* Euclidian norm of the three orthogonal acceleration signals) across all evoked movements. Finally, for visualization purposes, grand averages were computed across all individuals for dominant and non-dominant hands separately.

2.6. Statistical analysis

2.6.1. Statistical significance of coherence

The statistical significance of individual coherence levels (maximum value across a pre-selection of 40 gradiometers) was assessed under the hypothesis of linear independence of Fourier coefficients from epoch to epoch at each frequency of interest, taking into account the use of overlapping epochs (Halliday et al., 1995; Bourguignon et al., 2011). To correct for multiple comparisons, the alpha level was set to $0.05/(Nf \times Ns)$, $Nf = 1$ being the number of tested frequency bins (movement frequency and its first harmonic), and $Ns = 40$ the number of gradiometers included in the analysis.

2.6.2. Reproducibility, analysis of variance, and correlations

These statistical analyses were performed in IBM SPSS Statistics software (ver. 25). Data were first ensured to have normal distribution using the Shapiro-Wilk test. To enable comparison to other studies, we used two commonly used and closely related test to assess inter-session reproducibility for CKC strength and steady-state field amplitudes. Both Pearson correlation coefficient and two-way mixed-effects model intraclass-correlation coefficient (ICC) were computed between the Day-1 and Day-2 values.

CKC strength, steady-state field amplitude, number of averages and peak acceleration magnitudes were compared using a two-way 2 (*hands: dominant/non-dominant*) × 2 (*days*: *Day-1/Day-2*) repeated-measures analysis of variance (ANOVA).

In order to estimate associations between CKC strength, MEG signal amplitude, kinematics of the passive movement, Pearson correlation coefficients were computed across all individuals between CKC strength, steady-state field amplitude, and peak acceleration magnitude. In addition, Pearson correlation was computed between change in CKC strength and participants initial head position in MEG (separately for x-, y- and z-axis) from Day-1 to Day-2. The aim was to clarify whether small scale alterations in distance between the MEG sensors and the cortex affect the CKC strength.

All results are indicated as mean ± standard deviation.

3. Results

Fig. 2 shows continuous MEG and acceleration signals during 3-Hz index-finger movements for Participant 1. The actuator did not produce notable artifacts into the MEG signals. The acceleration signal contains two clear peaks during each movement cycle, reflecting the initiations of the flexion and extension phases. The fluctuation of the MEG signal at the movement frequency reflects mainly alterations in cortical oscillations due to afferent proprioceptive input. Fig. 3 shows grand averages of MEG and acceleration signals, and respective coherence spectra for the 3-Hz index-finger movements. Steady-state fields, movement kinematics and CKC were very similar between the two measurements separated by 12.6 ± 1.3 months.

All recordings were successful with 601 ± 20 and 595 ± 14 averages collected to dominant hand stimulation (Day-1 and Day-2, respectively), and 606 ± 20 and 607 ± 23 averages to non-dominant hand stimulation. There were no statistical differences in the number of averages between *days* ($F_{1,12} = 0.12$, $p = 0.735$) or *hands* ($F_{1,12} = 3.72$, $p = 0.078$), and no significant interaction ($F_{1,12} = 0.53$, $p = 0.479$). The participants' head was positioned in MEG with only few millimetre differences between the *days* (x-axis: 2.6 ± 2.0 mm, range 0.5–7.1 mm; y-axis: 3.4 ± 2.3 mm, 1.1–7.4 mm; z-axis: 3.7 ± 3.0 mm, 0.8–9.3 mm).

3.1. Kinematics

Fig. 3a shows grand average of acceleration magnitude signals. The

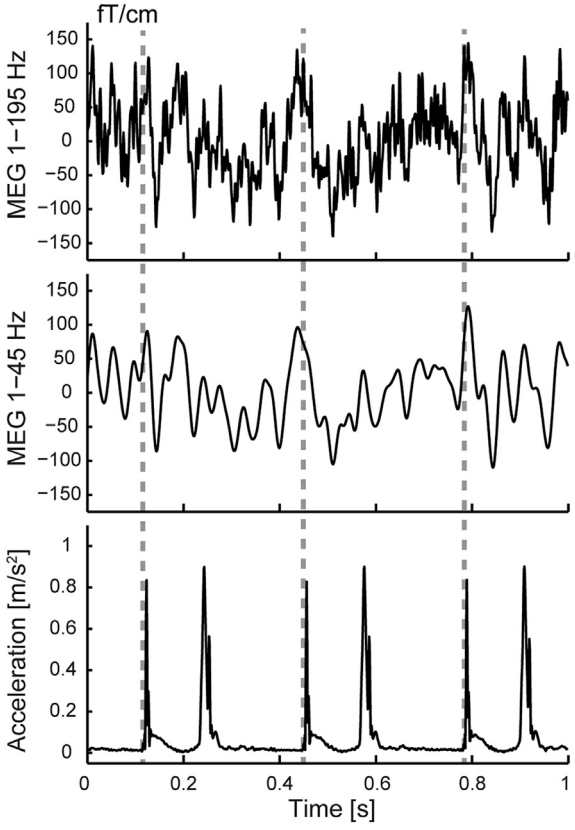

Fig. 2. Representative signals. Continuous, unaveraged 1–195-Hz and 1–45-Hz MEG (from the most responsive Rolandic channel) signals and acceleration-magnitude signal of Participant 1 during the 3-Hz passive movement. The grey dotted vertical lines indicate the onsets of the finger movements.

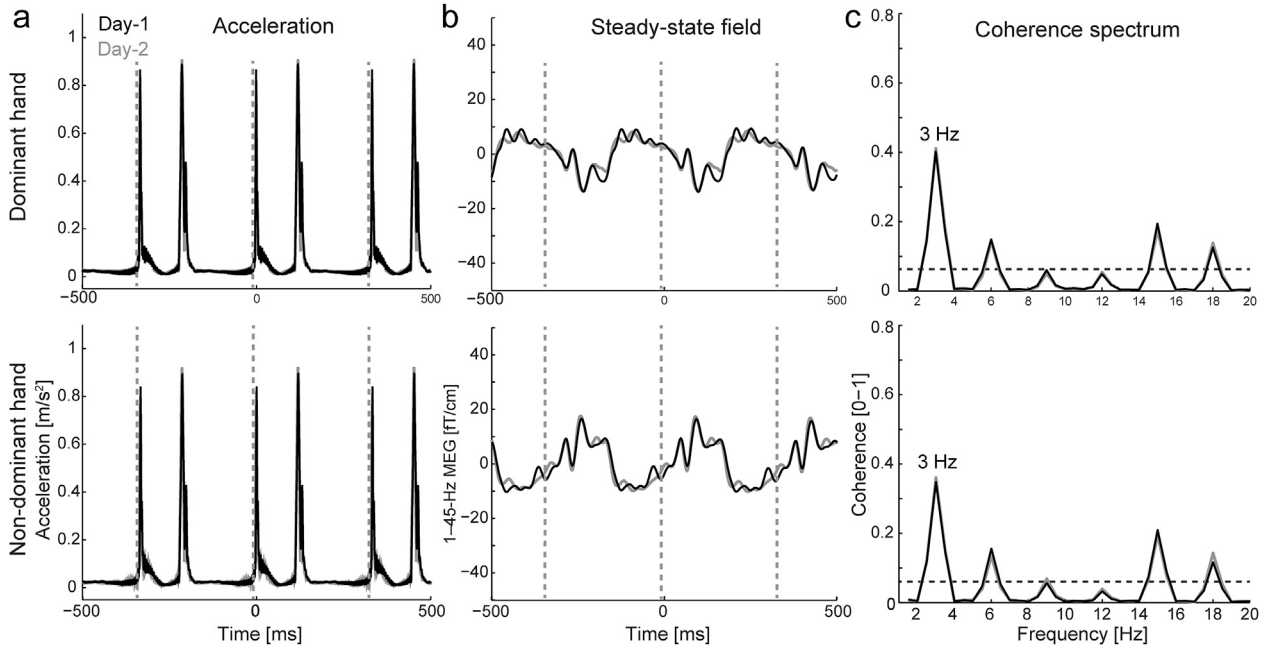

Fig. 3. Grand averages of (a) acceleration magnitude, (b) steady-state field, and (c) coherence spectra across all participants (n = 13). Black solid lines indicate Day-1 and grey ones Day-2 averages. Grey dashed vertical line indicates onsets of the movement stimuli. Black dashed horizontal line indicates threshold for statistical significance of corticokinematic coherence (CKC).

peak acceleration magnitude was at similar level at Day-1 and Day-2 for dominant (0.93 ± 0.04 m/s^2 vs. 0.92 ± 0.04 m/s^2) and non-dominant (0.91 ± 0.04 m/s^2 vs. 0.92 ± 0.04 m/s^2) hands. The peak acceleration magnitude did not differ between *days* ($F_{1,12} = 0.03$, $p = 0.959$) or *hands* ($F_{1,12} = 0.28$, $p = 0.604$), with no significant interaction ($F_{1,12} = 2.29$, $p = 0.156$). Coefficient of variation for the peak acceleration magnitude across the evoked movements was on average only 2.6 ± 0.8% at Day-1 and 1.9 ± 0.3% (hands pooled together).

3.2. Steady-state fields

Fig. 3b shows grand averages of the steady-state fields for dominant and non-dominant hands at the Day-1 and Day-2 for the same sensor in which the CKC peaked. The grand averages appeared very similar between the days. Steady-state field amplitudes did not differ significantly between *days* ($F_{1,12} = 0.01$, $p = 0.907$) or *hands* ($F_{1,12} = 0.03$, $p = 0.878$), and there was no significant interaction ($F_{1,12} = 0.01$, $p = 0.954$). For the dominant hand, the amplitude was 22.9 ± 7.6 fT/cm at Day-1 and 22.6 ± 9.4 fT/cm at Day-2. For the non-dominant hand, the amplitude was 22.8 ± 7.3 fT/cm at Day-1 and 22.4 ± 10.6 fT/cm at Day-2).

3.3. Corticokinematic coherence

Fig. 3c shows grand averages of CKC spectra for the 3-Hz index-finger movements at the Day-1 and Day-2. The CKC spectra overlapped well at the group level. Fig. 4 illustrates the topographic distribution of the CKC grand average for the dominant and non-dominant hands at Day-1 and Day-2. CKC peaked at sensors over the hand area of the SM1 cortex contralateral to the evoked-movements in good spatial accordance with sensors showing the strongest steady-state field response.

In the group level, CKC remained at similar level between Day-1 (dominant 0.40 ± 0.19; non-dominant 0.35 ± 0.16) and Day-2 (dominant 0.41 ± 0.17; non-dominant 0.36 ± 0.17). CKC strength did not differ between *days* ($F_{1,12} = 0.52$, $p = 0.486$) or *hands* ($F_{1,12} = 1.19$, $p = 0.298$), with no significant interactions (*days*hands* $F_{1,12} = 0.01$, $p = 0.928$).

3.4. Reproducibility

Fig. 5 illustrates change and scatterplots for individual CKC values between Day-1 to Day-2. In general, participants with strong CKC at Day-1 showed strong CKC also at Day-2 and *vice versa*. For the non-dominant hand, CKC strength was stable between the *days*, however, for the dominant hand, 6 out of 13 participants showed >0.1 unit alteration in their CKC strength. Table 1 presents the reproducibility values for CKC using three different MEG channel selection approaches. All Pearson correlation tests between Day-1 and Day-2 were significant and the respective ICC values indicated excellent (≥0.75) inter-session reproducibility for CKC strength both for dominant and non-dominant hands, and for all approaches.

When the dominant and non-dominant CKC values were pooled together the ICC was 0.96. In addition, reproducibility of CKC was excellent also for the first harmonic of the movement frequency (i.e. at 6-Hz) for dominant (0.84) and non-dominant (0.84) hands.

ICC values indicated excellent (≥0.75) inter-session reproducibility also for the steady-state field amplitudes for both dominant (0.86) and non-dominant (0.97) hands. Furthermore, the steady-state field amplitude correlated between the Day-1 and Day-2 recordings both for dominant ($r = 0.743$, $p = 0.004$) and non-dominant ($r = 0.949$, $p < 0.001$) hands.

3.5. Correlations between CKC, steady-state fields, kinematics and head position

Fig. 6 shows scatter diagrams for CKC strength and steady-state field amplitude. CKC strength correlated positively with steady-state field amplitude for non-dominant hand at Day-1 ($r = 0.700$, $p = 0.008$) and at Day-2 ($r = 0.638$, $p = 0.019$), and for dominant hand at Day-2 ($r = 0.657$, $p = 0.015$), however, not at Day-1 ($r = 0.471$, $p = 0.104$). The acceleration magnitude of the movement stimuli did not correlate with CKC strength or steady-state field amplitudes. Differences in head position in vertical (z) axis and CKC strength between Day-1 and Day-2 were correlated significantly for dominant hand ($r = -675$, $p = 0.011$), but not for non-dominant hand ($r = 0.271$, $p = 0.370$). *I.e.*, shift of the head further away from the parietal MEG sensors was associated with reduction in CKC strength and *vice versa*.

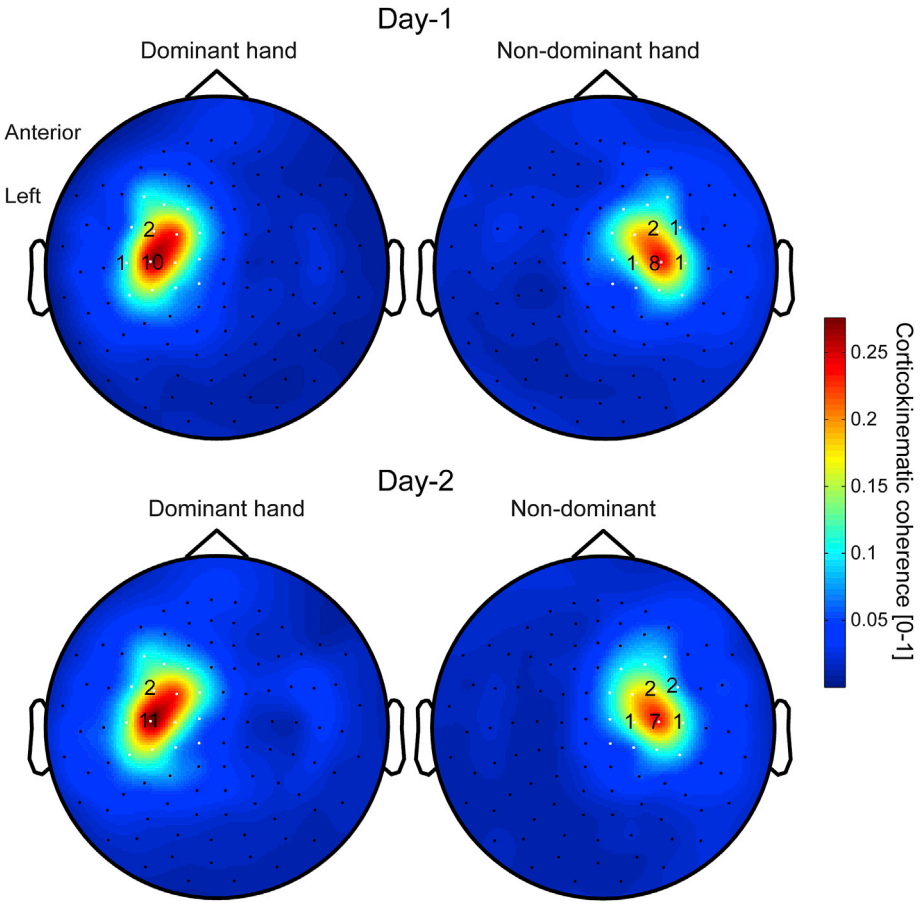

Fig. 4. Topographic distribution of the CKC grand average (n = 13) and locations of the peak steady-state field MEG sensors (superimposed black numbers) for dominant and non-dominant hands at Day-1 and Day-2. The superimposed numbers denote the sum of participants showing their peak steady-state field in a given MEG sensor. White dots indicate the 30-gradiometer selection used to obtain average CKC across the selection, separately for dominant and non-dominant hands.

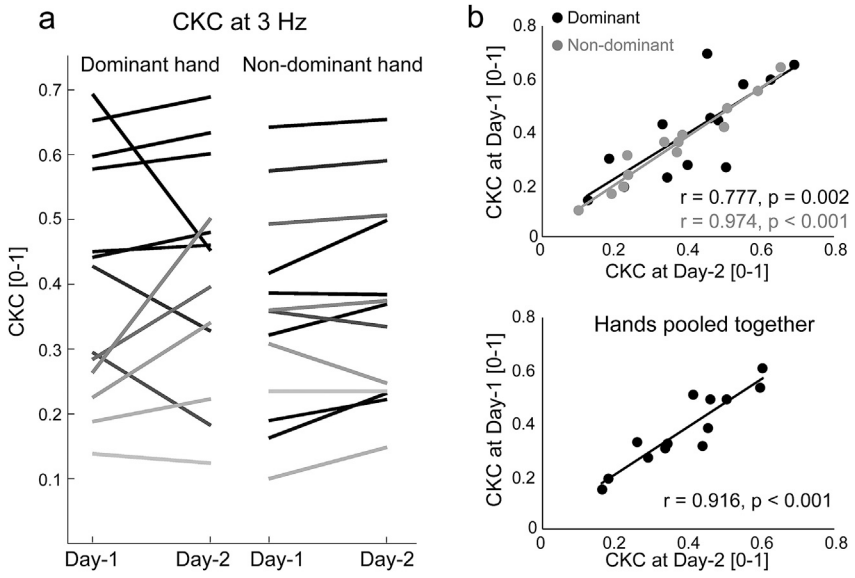

Fig. 5. Individual coherence values and correlation to MEG amplitude. (a) Solid lines indicate participant's peak CKC value at Day-1 and Day-2 for dominant and non-dominant hands at the 3-Hz-movement frequency. The solid lines are color coded in order of CKC-peak magnitude of dominant hand at Day-1. (b) Pearson correlation coefficient of CKC strength between Day-1 (y-axis) and Day-2 (x-axis) for dominant and non-dominant hands (upper panel), and when the hands were pooled together (lower panel).

4. Discussion

We examined reproducibility of CKC for passive index-finger movements elicited by the pneumatic movement actuator. We observed significant CKC in all studied participants, in accordance with earlier studies using passive movements evoked by movement actuators (Piitulainen et al., 2015, 2018). The reproducibility of CKC strength was excellent in the group level. However, in several participants, the inter-session variation was high, and thus caution needs to be taken if the aim is to follow single individuals or patients. CKC appears to be a potential tool for longitudinal studies to examine cortical proprioceptive processing. In addition, the respective steady-state fields were highly reproducible and

Table 1
Inter-session reproducibility of CKC.

	Dominant		Non-Dominant	
Approach	ICC	Pearson r	ICC	Pearson r
Single gradiometer	0.88	0.78**	0.99	0.97***
Gradiometer pair	0.78	0.63*	0.95	0.90***
30-gradiometer selection	0.83	0.69**	0.98	0.95***

* = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$.

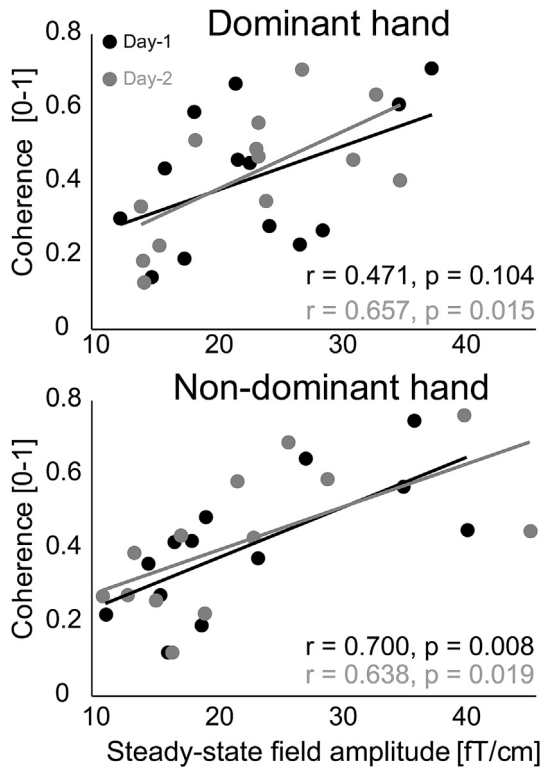

Fig. 6. Pearson correlation coefficient between CKC and respective MEG amplitude for dominant (upper panel) and non-dominant (lower panel) hands at Day-1 (in black) and Day-2 (in grey).

their amplitude was positively correlated with CKC strength.

4.1. Reproducibility of CKC

The pneumatic movement actuator evoked very reproducible passive movements from stimulus-to-stimulus, participant-to-participant, and session-to-session. The variation in the peak acceleration magnitude across stimuli was on average only ~2%. The kinematics did not correlate with CKC strength or steady-state field amplitude, and thus the inter-individual variation in the CKC strength was not due to variation in the kinematics of the evoked-passive movements. Pneumatic-movement actuators can thus be used as a reliable tool to provide repetitive stimuli for longitudinal studies of proprioceptive processing.

In line with previous studies, CKC showed high inter-individual variation (Bourguignon et al., 2011; Piitulainen et al., 2012, 2013a, 2015). For most participants, the CKC level remained stable during the 1-year follow-up. However, in the dominant hand inter-session reliability was higher than in the non-dominant hand. As reproducibility was quite similar for averaged CKC of several MEG sensors compared with the single sensor approach, the difference is not likely to result from the selection of MEG sensors in the analysis. Time of day of the recording session varied randomly from morning to evening, but did not seem to effect the inter-session variation systematically. As there are anatomical and functional differences between left and right SM1 cortices, it is possible that these differences may have affected the reproducibility of CKC.

Head orientation and distance with respect to the MEG sensors in individual measurement sessions may affect the signal-to-noise ratio of the MEG signals, and thus eventually the CKC strength. Although the individual head positions were very similar between the sessions (<10 mm), we found a significant correlation between the difference in vertical axis position of the head and CKC strength in the left SM1 cortex. As the head shifted away (i.e. downwards) from the parietal MEG sensors from Day-1 to Day-2, the CKC strength was reduced in the left SM1 cortex and *vice versa*. It was surprising that the effect of the head position was not equal between the hemispheres. The greater "vulnerability" of the left SM1 cortex MEG signals to small changes in head orientation and distance from the sensors may arise from anatomical and functional asymmetries between the left and right SM1 cortices due to hand dominance. For example, the surface area of the central sulcus is larger (White et al., 1994), functional motor cortex volume is wider (Volkmann et al., 1998) and motor representation is located more dorsally (Sun et al., 2012) in the dominant left hemisphere compared with the right. It is also possible that our sample size was too small to show similar association for the right SM1 cortex, especially since the head shifts were very small. Part of this variation can potentially be reduced by aligning the participants head position as accurately as possible between the repeated sessions.

Our findings are in line with some prior MEG studies that have found excellent inter-session reproducibility of somatosensory evoked responses (Ou et al., 2007; Schaefer et al., 2004). Source localizations of early somatosensory evoked fields to tactile stimulation are shown to be highly reproducible between sessions (separated by ~5 months) with less than 1 cm difference in their Euclidean distance (Schaefer et al., 2004). Similarly, the shape of the early somatosensory response to electric median-nerve stimulation has found to be highly similar between sessions (Ou et al., 2007). In contrast, the inter-session reproducibility (separated by ~1 year) of cortex-muscle coherence (CMC) strength has been shown to be low (Pohja et al., 2005). The source for high inter-session variation in CMC remains unclear, but can be affected by change in motor strategy, *e.g.,* due to fatigue or variability of the contraction force.

CKC records cortical processing of proprioceptive afference induced by passive movements, whereas the more widely used CMC is computed between MEG and electromyographic signals during sustained isometric-voluntary contraction and reflects the coupling between cortical motoneurons and muscular activity. Thus, CMC is suggested to reflect cortical motor efference to the spinal α-motoneurons and thus modulating population-level motor-unit discharges (Baker et al., 1997; Conway et al., 1995; Salenius et al., 1997), but reafferent contribution has also been argued (Witham et al., 2011). Therefore, CKC and CMC are quantifying different phenomena. However, the advantage of CKC is that it can extract the somatosensory component of the corticospinal coupling both during passive and dynamic voluntary movements (Bourguignon et al., 2015; Piitulainen et al., 2013a). Therefore, CKC is applicable also in paralyzed patients. CKC strength is typically 5–10-fold stronger than CMC strength, and thus can be detected in most if not all individuals, whereas significant CMC is sometimes too weak to be detected in all individuals (Pohja et al., 2005).

The excellent reproducibility of CKC at group level enables its use in longitudinal studies, but alterations in CKC values, *e.g.*, in individual patients should be interpreted with caution. Since CKC primarily reflects proprioceptive processing in the SM1 cortex (Bourguignon et al., 2015; Piitulainen et al., 2013a) it may be useful to follow changes in cortical proprioceptive processing, *e.g.*, during stroke recovery, motor-skill acquisition, sensorimotor development, and aging. The correlation between CKC strength and behavior, *i.e.*, functional motor performance could also be studied in future longitudinal designs utilizing CKC. However, measurement of CKC requires special movement actuators that should be made better available. The principle and use of the actuators

are simple, and thus they can easily be made available similarly as, *e.g.*, tactile stimulators. Finally, there is no reason to doubt that CKC could also be reliably measured with EEG thus expanding opportunities for research and clinical use of the CKC method.

4.2. Effect of steady-state field amplitude and kinematics to CKC

All individuals showed robust significant CKC at the movement frequency. However, inter-individual variation was high in line with the previous studies (Bourguignon et al., 2011; Piitulainen et al., 2012, 2013a, 2015). The individuals with strongest CKC showed up to ~7 fold CKC strength than the one with weakest CKC (range 0.10–0.69).

Based on simulations, coherence strength is positively associated with signal-to-noise ratio in noisy signals (Muthukumaraswamy and Singh, 2011). MEG can be considered as noisy signal, since in addition to sensor noise there is also unavoidable physiological noise, including the "brain noise". Therefore, the CKC strength may be partly dependent on signal-to-noise ratio of the MEG signal. Indeed, for the most part of the data, the CKC strength showed positive association with the steady-state field amplitude, *i.e.*, the stronger the stimulus-related-MEG signal was the stronger was the CKC. This finding is in accordance with the previous suggestion that CKC reflects coupling between the strongest deflection of the steady-state field and the acceleration signal (Piitulainen et al., 2015). However, the steady-state field amplitude does not solely explain the inter-individual differences in CKC, as this association was insignificant for the dominant hand, and has not been observed for CKC recorded from the lower limbs (Piitulainen et al., 2018). Furthermore, this recent study suggested association between motor performance and CKC strength. Standing postural performance that is relying strongly on proprioception was predicted by the CKC strength of the lower limbs (Piitulainen et al., 2018). This implies that substantial part of the inter-individual variation in CKC strength may be due to differences in cortical proprioceptive processing.

MEG response amplitudes are affected by inter-individual differences in anatomy. For example, MEG sensitivity is weaker for more deeper sources or sources oriented more radially to the skull surface (Hillebrand and Barnes, 2002). Thus, part of the inter-individual variation in CKC strength is likely due to anatomical variations.

4.3. Limitations

The passive movement stimuli activated proprioceptors (muscle afferents), and inevitably mechanoreceptors of the skin. However, cutaneous stimuli do not have significant effects on the CKC strength during passive index-finger movements (Bourguignon et al., 2015; Piitulainen et al., 2013a), and thus, the results reflect primarily cortical processing of the proprioceptive afference.

As the current results indicated, CKC strength can be estimated in sensor level with high reproducibility. We restricted the analysis on sensor level, because, previous studies have already shown that source localizations of somatosensory evoked fields are highly reproducible between sessions separated by several months (Schaefer et al., 2004). Restricting the analysis to sensor level enables efficient data processing with minimal number of confounding factors. This straightforward approach is an advantage in potential future applications of CKC. However, to compensate for possible changes in head coordinates between the sessions, we transferred the coordinates to average (of Day-1 and Day-2 coordinates) reference head position during the temporal signal-space-separation (Taulu and Simola, 2006). For the same reason, single MEG gradiometer showing the strongest CKC was defined separately for each session. This approach produced the highest reproducibility ICC and Pearson correlations between the sessions, and can thus be recommended for future studies. As discussed above, some caution need to be taken when following up the CKC strength at the individual level, especially for the dominant hand.

The study group composed of young adults, and thus cannot be readily generalized to populations comprised of older adults that might have emerging or ongoing aging related deterioration of their sensorimotor systems, such as impaired proprioceptive sensibility (Goble et al., 2009). Although, the absolute level of CKC is clearly different for younger than older adults (Piitulainen et al., 2018), further longitudinal studies are required to examine the sensitivity of the CKC method to detect minute adaptations in cortical proprioceptive processing during normal aging.

The reproducibility of the steady-state fields was also excellent. However, our analysis was not optimized to study reproducibility of the steady-state fields, but to examine association between CKC strength and steady-state field amplitude. For this reason, the steady-state field amplitude was computed from the same sensor that showed the strongest CKC, but this sensor was not always the one showing the strongest steady-state response (~35% of the cases).

5. Conclusions

Our results imply that reproducibility of the CKC strengths is excellent in the group level when using MEG and pneumatic passive movement actuator. Thus, CKC approach shows potential as tool to follow the cortical proprioceptive processing in longitudinal studies. However, caution needs to be taken if the aim is to follow single individuals. We also found that the CKC strength is associated with the strength of the corresponding cortical responses. Future studies should examine the potential of CKC to follow changes in cortical proprioceptive processing in individual level, and associations to concomitant changes in motor performance.

Funding

This study has been supported by the Academy of Finland (grants #296240, #307250 and #304294) to HP, Jane and Aatos Erkko Foundation, and Eemil Aaltonen Foundation to HP, and TEKES Seamless patient care project to KL.

Declarations of interest

None.

Acknowledgements

We thank technical support from Helge Kainulainen and Ronny Schreiber at Aalto NeuroImaging.

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